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STN INTERNATIONAL LOGOFF AT 15:15:43 ON 21 JAN 2004


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* * * * * * * * * *   Welcome to STN International   * * * * * * * * * *

 NEWS  1          Web Page URLs for STN Seminar Schedule - N. America
 NEWS  2          "Ask CAS" for self-help around the clock
 NEWS  3  JAN 27  Source of Registration (SR) information in REGISTRY updated
                  and searchable
 NEWS  4  JAN 27  A new search aid, the Company Name Thesaurus, available in
                  CA/CAplus
 NEWS  5  FEB 05  German (DE) application and patent publication number format
                  changes
 NEWS  6  MAR 03  MEDLINE and LMEDLINE reloaded
 NEWS  7  MAR 03  MEDLINE file segment of TOXCENTER reloaded
 NEWS  8  MAR 03  FRANCEPAT now available on STN
 NEWS  9  MAR 29  Pharmaceutical Substances (PS) now available on STN
 NEWS 10  MAR 29  WPIFV now available on STN
 NEWS 11  MAR 29  New monthly current-awareness alert (SDI) frequency in RAPRA
 NEWS 12  APR 26  PROMT: New display field available
 NEWS 13  APR 26  IFIPAT/IFIUDB/IFICDB: New super search and display field
                  available
 NEWS 14  APR 26  LITALERT now available on STN
 NEWS 15  APR 27  NLDB: New search and display fields available
 NEWS 16  May 10  PROUSDDR now available on STN
 NEWS 17  May 19  PROUSDDR: One FREE connect hour, per account, in both May
                  and June 2004
 NEWS 18  May 12  EXTEND option available in structure searching
 NEWS 19  May 12  Polymer links for the POLYLINK command completed in REGISTRY
 NEWS 20  May 17  FRFULL now available on STN

 NEWS EXPRESS  MARCH 31 CURRENT WINDOWS VERSION IS V7.00A, CURRENT
               MACINTOSH VERSION IS V6.0c(ENG) AND V6.0Jc(JP),
               AND CURRENT DISCOVER FILE IS DATED 26 APRIL 2004
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FILE 'HOME' ENTERED AT 15:52:51 ON 19 MAY 2004

=> b medline caplus lifesci embase uspatfull biosis
COST IN U.S. DOLLARS                            SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                 0.21       0.21

FILE 'MEDLINE' ENTERED AT 15:53:07 ON 19 MAY 2004

FILE 'CAPLUS' ENTERED AT 15:53:07 ON 19 MAY 2004
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PLEASE SEE "HELP USAGETERMS" FOR DETAILS.


FILE 'LIFESCI' ENTERED AT 15:53:07 ON 19 MAY 2004


FILE 'EMBASE' ENTERED AT 15:53:07 ON 19 MAY 2004


FILE 'USPATFULL' ENTERED AT 15:53:07 ON 19 MAY 2004


FILE 'BIOSIS' ENTERED AT 15:53:07 ON 19 MAY 2004


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=> s propylxanthine
L1          620 PROPYLXANTHINE

=> s 3()n() propylxanthine
L2           48 3(W) N(W) PROPYLXANTHINE

=> dup rem l2
PROCESSING COMPLETED FOR L2
L3           32 DUP REM L2 (16 DUPLICATES REMOVED)

=> s l3 and adenosine receptor
L4            7 L3 AND ADENOSINE RECEPTOR

=> d l4 ibib abs tot

L4   ANSWER 1 OF 7     MEDLINE on STN
ACCESSION NUMBER:    2001700409     MEDLINE
DOCUMENT NUMBER:     PubMed ID: 11726639
TITLE:                 ***Adenosine***     ***receptor***   antagonists and
                     retinal neovascularization in vivo.
AUTHOR:              Mino R P; Spoerri P E; Caballero S; Player D; Belardinelli
                     L; Biaggioni I; Grant M B
CORPORATE SOURCE:    Department of Molecular Biology and Genetics, University of
                     Florida, Gainesville, FL 32610-0267, USA.
SOURCE:              Investigative ophthalmology & visual science, (2001 Dec) 42
                     (13) 3320-4.
                     Journal code: 7703701. ISSN: 0146-0404.
PUB. COUNTRY:        United States
DOCUMENT TYPE:       Journal; Article; (JOURNAL ARTICLE)
LANGUAGE:            English
FILE SEGMENT:        Priority Journals; Space Life Sciences
ENTRY MONTH:         200201
ENTRY DATE:          Entered STN: 20011220
                     Last Updated on STN: 20020216
                     Entered Medline: 20020115
AB   PURPOSE: The role of   ***adenosine***     ***receptor***   (AdoR)
     antagonists in human retinal endothelial cell function in vitro has
     previously been determined.  In this study, efficacy of AdoR antagonist
     administration in reducing retinal neovascularization was examined in a
     mouse pup model of oxygen-induced retinopathy.  METHODS: A previously
     described model of oxygen-induced retinal neovascularization in newborn
     mouse pups was used to examine the effect of various AdoR antagonists on
     neovascularization.  The nonselective AdoR antagonist xanthine amine
     congener (XAC), the A(2A)-selective antagonist ZM241385, the
     A(2B)-selective antagonists   ***3***  -  ***N***  -  ***propylxanthine***
     (enprofylline) and 3-isobutyl-8-pyrrolidinoxanthine (IPDX), and the
     A(1)-selective antagonist cyclopentyl-1,3-dipropylxanthine (CPX) were
     used.  After the hyperoxia exposure the animals received daily
     intraperitoneal injections of pharmacologically relevant doses of AdoR
     antagonists for 5 days.  Control animals received vehicle (0.1% dimethyl
     sulfoxide [DMSO]) alone.  The animals were then killed and perfused with
     fluorescein-dextran.  Wholemounts of retinas from one eye were prepared
     and examined, whereas the retinas of the contralateral eye were embedded,
     sectioned, and stained for counting neovascular nuclei extending beyond
     the internal limiting membrane into the vitreous.  RESULTS: Angiography of
     wholemount retinas showed reduction of neovascular tufts in animals
     treated with selective A(2B) AdoR antagonists.  Quantification of the
     extraretinal neovascular nuclei showed that only animals treated with XAC,
     enprofylline, or IPDX showed a significant reduction in retinal
     neovascularization.  By contrast, neither CPX nor ZM241385 had an effect
     on neovascularization.  CONCLUSIONS: The A(2B)-selective AdoR antagonists
```

provide a basis for developing pharmacologic therapies for the treatment of proliferative retinopathies.

L4 ANSWER 2 OF 7 MEDLINE on STN
ACCESSION NUMBER: 2001433635 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11481274
TITLE: Proliferation, migration, and ERK activation in human retinal endothelial cells through A(2B) ***adenosine*** ***receptor*** stimulation.
AUTHOR: Grant M B; Davis M I; Caballero S; Feoktistov I; Biaggioni I; Belardinelli L
CORPORATE SOURCE: Department of Medicine, University of Florida, Gainesville 32610-0267, USA.. grantma@pharmacology.ufl.edu
SOURCE: Investigative ophthalmology & visual science, (2001 Aug) 42 (9) 2068-73.
Journal code: 7703701. ISSN: 0146-0404.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010820
Last Updated on STN: 20010820
Entered Medline: 20010816

AB PURPOSE: The nucleoside adenosine has been implicated in angiogenesis. A previous study demonstrated that activation of the A(2B) ***adenosine*** ***receptor*** (AdoR) increases cAMP accumulation, cell proliferation, and VEGF expression in human retinal endothelial cells (HRECs). In the present study, the role of this receptor was further characterized by examination of the effects of the selective A(2B) AdoR antagonists ***3*** - ***N*** - ***propylxanthine*** (enprofylline) and 3-isobutyl-8-pyrrolidinoxanthine (IPDX) on AdoR-mediated HREC proliferation, capillary tube formation, and signal-transduction pathways. METHODS: HRECs were exposed to the adenosine analogue 5'-N-ethylcarboxamido-adenosine (NECA) in the absence or presence of AdoR antagonists. Migration was measured using Boyden chambers. Proliferation was assessed by counting cells. Western analysis was used to assess extracellular signal-related kinase (ERK) and cAMP response element-binding protein (CREB) in cell lysates. The effect of AdoR activation on tube formation was studied using cells grown on a synthetic basement membrane matrix. RESULTS: NECA induced proliferation in a concentration-dependent manner that was inhibited by enprofylline and IPDX. NECA stimulated chemotaxis in a concentration-dependent manner that was also blocked by both A(2B) AdoR antagonists. NECA activated ERK and CREB in HRECs. Both A(2B) AdoR antagonists diminished activation of ERK by NECA exposure. ERK activation was also blocked by the ERK-mitogen-activated protein kinase (MAPK) inhibitor PD98059, but not by the protein kinase A (PKA) inhibitor H-89. CREB activation was blocked by H-89, but not by PD98059, suggesting that ERK activation is independent of PKA. NECA enhanced tube formation on the matrix, whereas both A(2B) AdoR antagonists attenuated this effect. CONCLUSIONS: The selective A(2B) AdoR antagonists, enprofylline and IPDX, inhibited NECA-stimulated proliferation, ERK activation, cell migration, and capillary tube formation. A(2B) AdoR inhibition may offer a way to inhibit retinal angiogenesis and provide a novel therapeutic approach to treatment of diseases associated with aberrant neovascularization, such as diabetic retinopathy and retinopathy of prematurity.

L4 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:304316 CAPLUS
DOCUMENT NUMBER: 132:318044
TITLE: Method for improving insulin sensitivity using an ***adenosine*** ***receptor*** antagonist
INVENTOR(S): Lanoue, Kathryn F.; Crist, George H.; Linden, Joel M.
PATENT ASSIGNEE(S): The Penn State Research Foundation, USA
SOURCE: U.S., 22 pp., Cont.-in-part of U.S. Ser. No. 86,101, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6060481 | A | 20000509 | US 1999-259201 | 19990301 |

AB The invention relates to methods for improving insulin sensitivity in a patient using one or more A2B ***adenosine*** ***receptor*** antagonists [e.g. ***3*** - ***n*** - ***propylxanthine*** ] are disclosed. These methods stimulate insulin dependent glucose uptake in muscle.
REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 7 USPATFULL on STN
ACCESSION NUMBER: 2004:7842 USPATFULL
TITLE: 2-Aminopyridine compounds and use thereof as drugs
INVENTOR(S): Harada, Hitoshi, Ibaraki, JAPAN
Asano, Osamu, Ibaraki, JAPAN
Miyazawa, Shuhei, Ibaraki, JAPAN
Ueda, Masato, Ibaraki, JAPAN
Yasuda, Masahiro, Ibaraki, JAPAN
Yasuda, Nobuyuki, Ibaraki, JAPAN

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2004006082 | A1 | 20040108 | |
| APPLICATION INFO.: | US 2003-333689 | A1 | 20030123 | (10) |
| | WO 2001-JP6870 | | 20010809 | |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | JP 2000-245056 | 20000811 |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
LINE COUNT: 3562
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides 2-aminopyridine compound having an excellent ***adenosine*** ***receptor*** (A.sub.1, A.sub.2a, A.sub.2b receptors) antagonism, which is represented by the following formula: ##STR1##

(wherein, R.sup.1 represents cyano group, carboxyl group or an optionally substituted carbamoyl group; R.sup.2 represents hydrogen atom, hydroxyl group, an optionally substituted C.sub.1-6 alkoxy group, an optionally substituted C.sub.6-14 aromatic hydrocarbon cyclic group or an optionally substituted 5- to 14-membered aromatic heterocyclic group; and R.sup.3 and R.sup.4 are the same as or different from each other and each represents a C.sub.6-14 aromatic hydrocarbon cyclic group, a 5- to 14-membered non-aromatic heterocyclic group or a 5- to 14-membered aromatic heterocyclic group which may be substituted, respectively) or a salt thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 5 OF 7 USPATFULL on STN
ACCESSION NUMBER: 2003:244969 USPATFULL
TITLE: Medicinal compositions promoting bowel movement
INVENTOR(S): Yasuda, Masahiro, Ibaraki, JAPAN
Harada, Hitoshi, Ibaraki, JAPAN
Miyazawa, Shuhei, Ibaraki, JAPAN
Kobayashi, Seiichi, Belmont, MA, UNITED STATES
Harada, Kokichi, Ibaraki, JAPAN
Hida, Takayuki, Ibaraki, JAPAN
Shibata, Hisashi, Ibaraki, JAPAN
Yasuda, Nobuyuki, Ibaraki, JAPAN
Asano, Osamu, Ibaraki, JAPAN
Kotake, Yoshihiko, Ibaraki, JAPAN

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2003171383 | A1 | 20030911 | |
| APPLICATION INFO.: | US 2002-257091 | A1 | 20021009 | (10) |
| | WO 2001-JP3643 | | 20010426 | |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | JP 2000-126489 | 20000426 |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747
NUMBER OF CLAIMS: 31
EXEMPLARY CLAIM: 1
LINE COUNT: 2491
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB The present invention provides a medicament having a gentle but strong defecation-promoting action without causing diarrhea. That is, it provides a defecation-promoting agent comprising a compound having an adenosine A.sub.2 receptor antagonism, preferably an adenosine A.sub.2b receptor antagonism, or a salt thereof.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 6 OF 7 USPATFULL on STN
ACCESSION NUMBER: 2002:4163 USPATFULL
TITLE: Method for identifying and using A2B ***adenosine*** ***receptor*** antagonists to mediate mammalian cell proliferation
INVENTOR(S): Belardinelli, Luiz, Menlo Park, CA, UNITED STATES
Grant, Maria B., Archer, FL, UNITED STATES

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2002002142 | A1 | 20020103 |
| APPLICATION INFO.: | US 2001-785895 | A1 | 20010216 (9) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 2000-183141P | 20000217 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: A. Blair Hughes, McDonnell Boehnen Hulbert & Berghoff, 32nd Floor, 300 S. Wacker Drive, Chicago, IL, 60606
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 453
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB This invention concerns methods for identifying A.sub.2B ***adenosine*** ***receptor*** agonists and antagonists as well as methods for using A.sub.2B. ***adenosine*** ***receptor*** antagonists to treat cell proliferation orders mediated by the A.sub.2B ***adenosine*** ***receptor*** .

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

L4 ANSWER 7 OF 7 USPATFULL on STN
ACCESSION NUMBER: 88:72477 USPATFULL
TITLE: 8-arylxanthines
INVENTOR(S): Rzeszotarski, Waclaw J., Millersville, MD, United States
Hicks, Rickey P., Columbia, MD, United States
Erickson, Ronald H., Baltimore, MD, United States
PATENT ASSIGNEE(S): Marion Laboratories, Inc., Kansas City, MO, United States (U.S. corporation)

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 4783530 | | 19881108 |
| APPLICATION INFO.: | US 1987-108990 | | 19871001 (7) |

RELATED APPLN. INFO.: Continuation-in-part of Ser. No. US 1986-931620, filed on 13 Nov 1986, now abandoned
DOCUMENT TYPE: Utility
FILE SEGMENT: Granted
PRIMARY EXAMINER: Rizzo, Nicholas S.
LEGAL REPRESENTATIVE: Dewey, Ballantine, Busby, Palmer & Wood
NUMBER OF CLAIMS: 8
EXEMPLARY CLAIM: 1
LINE COUNT: 705
CAS INDEXING IS AVAILABLE FOR THIS PATENT.
AB 1,3-alkylsubstituted-8-(3,4-,3- or 4-substituted phenyl)xanthines and pharmaceutically acceptable salts of such compounds are disclosed. The 3-substituents are hydrogen, dimethylaminomethyl, or

cyano, --NHCON(R.sub.5).sub.2, --C(.dbd.NH)N(R.sub.5).sub.2, --NH--C(.dbd.NH)N(R.sub.5).sub.2, with each R.sub.5 independently being hydrogen or an alkyl group of one to three carbons and provided that when the 3-substituent is hydrogen the 4-substituent is not hydroxy or hydrogen.

The compounds are potent ***adenosine*** ***receptor*** antagonists having relatively low lipophilicity. The compounds are intended for use as bronchodilators and cardiotonics.

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

=> d ibib kwic tot

L4 ANSWER 1 OF 7 MEDLINE on STN
ACCESSION NUMBER: 2001700409 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11726639
TITLE: ***Adenosine*** ***receptor*** antagonists and retinal neovascularization in vivo.
AUTHOR: Mino R P; Spoerri P E; Caballero S; Player D; Belardinelli L; Biaggioni I; Grant M B
CORPORATE SOURCE: Department of Molecular Biology and Genetics, University of Florida, Gainesville, FL 32610-0267, USA.
SOURCE: Investigative ophthalmology & visual science, (2001 Dec) 42 (13) 3320-4.
Journal code: 7703701. ISSN: 0146-0404.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Space Life Sciences
ENTRY MONTH: 200201
ENTRY DATE: Entered STN: 20011220
Last Updated on STN: 20020216
Entered Medline: 20020115
TI ***Adenosine*** ***receptor*** antagonists and retinal neovascularization in vivo.
AB PURPOSE: The role of ***adenosine*** ***receptor*** (AdoR) antagonists in human retinal endothelial cell function in vitro has previously been determined. In this study, efficacy of AdoR. . . various AdoR antagonists on neovascularization. The nonselective AdoR antagonist xanthine amine congener (XAC), the A(2A)-selective antagonist ZM241385, the A(2B)-selective antagonists ***3*** - ***N*** - ***propylxanthine*** (enprofylline) and 3-isobutyl-8-pyrrolidinoxanthine (IPDX), and the A(1)-selective antagonist cyclopentyl-1,3-dipropylxanthine (CPX) were used. After the hyperoxia exposure the animals received daily. . .

L4 ANSWER 2 OF 7 MEDLINE on STN
ACCESSION NUMBER: 2001433635 MEDLINE
DOCUMENT NUMBER: PubMed ID: 11481274
TITLE: Proliferation, migration, and ERK activation in human retinal endothelial cells through A(2B) ***adenosine*** ***receptor*** stimulation.
AUTHOR: Grant M B; Davis M I; Caballero S; Feoktistov I; Biaggioni I; Belardinelli L
CORPORATE SOURCE: Department of Medicine, University of Florida, Gainesville 32610-0267, USA.. grantma@pharmacology.ufl.edu
SOURCE: Investigative ophthalmology & visual science, (2001 Aug) 42 (9) 2068-73.
Journal code: 7703701. ISSN: 0146-0404.
PUB. COUNTRY: United States
DOCUMENT TYPE: Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 200108
ENTRY DATE: Entered STN: 20010820
Last Updated on STN: 20010820
Entered Medline: 20010816
TI Proliferation, migration, and ERK activation in human retinal endothelial cells through A(2B) ***adenosine*** ***receptor*** stimulation.
AB PURPOSE: The nucleoside adenosine has been implicated in angiogenesis. A previous study demonstrated that activation of the A(2B) ***adenosine*** ***receptor*** (AdoR) increases cAMP accumulation, cell proliferation, and VEGF expression in human retinal endothelial cells (HRECs). In the present study, the role of this receptor was further characterized by

***3*** - ***N*** - ***propylxanthine*** (enprofylline) and 3-isobutyl-8-pyrrolidinoxanthine (IPDX) on AdoR-mediated HREC proliferation, capillary tube formation, and signal-transduction pathways. METHODS: HRECs were exposed to the. . .

L4 ANSWER 3 OF 7 CAPLUS COPYRIGHT 2004 ACS on STN
ACCESSION NUMBER: 2000:304316 CAPLUS
DOCUMENT NUMBER: 132:318044
TITLE: Method for improving insulin sensitivity using an ***adenosine*** ***receptor*** antagonist
INVENTOR(S): Lanoue, Kathryn F.; Crist, George H.; Linden, Joel M.
PATENT ASSIGNEE(S): The Penn State Research Foundation, USA
SOURCE: U.S., 22 pp., Cont.-in-part of U.S. Ser. No. 86,101, abandoned.
CODEN: USXXAM
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

| PATENT NO. | KIND | DATE | APPLICATION NO. | DATE |
|---|---|---|---|---|
| US 6060481 | A | 20000509 | US 1999-259201 | 19990301 |
| PRIORITY APPLN. INFO.: | | | US 1998-86101 | 19980528 |

REFERENCE COUNT: 10 THERE ARE 10 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

TI Method for improving insulin sensitivity using an ***adenosine*** ***receptor*** antagonist
AB The invention relates to methods for improving insulin sensitivity in a patient using one or more A2B ***adenosine*** ***receptor*** antagonists [e.g. ***3*** - ***n*** - ***propylxanthine*** ] are disclosed. These methods stimulate insulin dependent glucose uptake in muscle.
ST insulin sensitivity ***adenosine*** ***receptor*** antagonist
IT Adenosine receptors
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antagonists; method for improving insulin sensitivity using an ***adenosine*** ***receptor*** antagonist)
IT Antidiabetic agents
(method for improving insulin sensitivity using an ***adenosine*** ***receptor*** antagonist)
IT 9004-10-8, Insulin, biological studies
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); BSU (Biological study, unclassified); BIOL (Biological study); OCCU (Occurrence)
(method for improving insulin sensitivity using an ***adenosine*** ***receptor*** antagonist)
IT 41078-02-8 89073-57-4 96865-92-8, Xanthine amine congener 102146-07-6 121496-66-0 166181-76-6
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(method for improving insulin sensitivity using an ***adenosine*** ***receptor*** antagonist)

L4 ANSWER 4 OF 7 USPATFULL on STN
ACCESSION NUMBER: 2004:7842 USPATFULL
TITLE: 2-Aminopyridine compounds and use thereof as drugs
INVENTOR(S): Harada, Hitoshi, Ibaraki, JAPAN
Asano, Osamu, Ibaraki, JAPAN
Miyazawa, Shuhei, Ibaraki, JAPAN
Ueda, Masato, Ibaraki, JAPAN
Yasuda, Masahiro, Ibaraki, JAPAN
Yasuda, Nobuyuki, Ibaraki, JAPAN

| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2004006082 | A1 | 20040108 | |
| APPLICATION INFO.: | US 2003-333689 | A1 | 20030123 | (10) |
| | WO 2001-JP6870 | | 20010809 | |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | JP 2000-245056 | 20000811 |

FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747
NUMBER OF CLAIMS: 40
EXEMPLARY CLAIM: 1
LINE COUNT: 3562
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention provides 2-aminopyridine compound having an excellent ***adenosine*** ***receptor*** (A.sub.1, A.sub.2a, A.sub.2b receptors) antagonism, which is represented by the following formula: ##STR1##

SUMM . . . the large intestine and in the eyeballs, lung, uterus and bladder (Br. J. Pharmacol., 118, 1461-1468 (1996)). The reason that ***adenosine*** ***receptor*** subtypes can exhibit their inherent functions is attributable to a difference in their distribution in tissues, a difference in topical. . . diseases in the neutral nerves, cardiovascular diseases, inflammatory diseases, diseases in the respiratory organs, immune diseases, etc., so usefulness of ***adenosine*** ***receptor*** agonists/antagonists against these diseases is expected. On one hand, important reports have been made in recent years on the relationship. . .

SUMM [0004] ***3*** - ***n*** - ***Propylxanthine*** , Theophylline, Caffeine, ##STR3##

SUMM . . . 5- and 6-positions of the pyridine ring are substituted with phenyl groups. However, the relationship of these compounds with an ***adenosine*** ***receptor*** is not described or suggested, and is not known at all.

SUMM [0019] As described above, those compounds having an antagonism to an ***adenosine*** ***receptor*** , particularly an antagonism to an adenosine A.sub.2 receptor (especially A.sub.2b receptor), are expected to exhibit an excellent action as pharmaceutical preparations and desired to be provided. However, those compounds having an excellent antagonism to an ***adenosine*** ***receptor*** and also acting effectively as a medicament have never been found. Accordingly, the object of the present invention is to. . . find, the receptor inhibiting compound which is useful as an agent for treating or preventing a disease to which an ***adenosine*** ***receptor*** (particularly A.sub.2 receptor, A.sub.2b receptor) relates.

SUMM . . . a salt thereof is useful not only as an agent for treating, preventing or improving a disease to which an ***adenosine*** ***receptor*** , particularly A.sub.2 receptor, especially A.sub.2B receptor, relates, for example, constipation, irritable bowel syndrome, constipation accompanying irritable bowel syndrome, organic constipation,. . .

SUMM . . . the composition according to the above-mentioned (24), which is an agent for treating or preventing a disease to which an ***adenosine*** ***receptor*** relates; (26) the composition according to the above-mentioned (24), which is an agent for treating or preventing a disease to. . . a disease to which an adenosine A.sub.2B receptor relates; (28) the composition according to the above-mentioned (24), which is an ***adenosine*** ***receptor*** antagonist; (29) the composition according to claim 24, which is an adenosine A.sub.2 receptor antagonist; (30) the composition according to. . .

SUMM . . . compound or a pharmacologically acceptable salt thereof for producing an agent for treating or preventing a disease to which an ***adenosine*** ***receptor*** relates, and a method of treating or preventing a disease to which an ***adenosine*** ***receptor*** relates, by administering a pharmacologically effective dose of the above-mentioned compound or a pharmacologically acceptable salt thereof to a patient.

SUMM [0030] In this specification, the "disease to which an ***adenosine*** ***receptor*** relates" means a disease to which an adenosine A.sub.1 receptor, A.sub.2a receptor, A.sub.2b receptor or A.sub.3 receptor relates. For example,. . .

SUMM . . . be provided. The compounds according to the present invention or a salt thereof have an excellent antagonistic action on an ***adenosine*** ***receptor*** (adenosine A.sub.1, A.sub.2a, A.sub.2b or A.sub.3 receptor), and are excellent as an antagonist for an adenosine A.sub.2 receptor, particularly for. . . present invention or a salt thereof are useful as an agent for treating or preventing a disease to which an ***adenosine*** ***receptor*** (adenosine A.sub.1, A.sub.2a, A.sub.2b or A.sub.3 receptor) relates, and a disease against which an antagonist for the receptor is efficacious.. . .

DETD [0404] The compound of the present invention represented by the above formula (I) is useful as an ***adenosine*** ***receptor*** (A.sub.1, A.sub.2a, A.sub.2b or A.sub.3 receptor) antagonist,

usefulness of the compound. . .

DETD [0411] The ability of the compound according to the present invention to bind to or the ability to inhibit ***adenosine*** ***receptor*** are as follows.

TABLE 1

| Test Compound | Ki (nM) A1 | Ki (nM) A2a | IC.sub.50 (nM) A2b |
|---|---|---|---|
| Example 1 | 990. . . | | |

DETD [0412] The compound according to the present invention or a salt thereof exhibited an excellent inhibitory activity on ***adenosine*** ***receptor***.

DETD . . . of the adenosine A.sub.2b receptor-inhibiting compound which was identified by measuring the binding ability and inhibitory ability thereof to the ***adenosine*** ***receptor*** in Test Example 1, a salt thereof, a hydrate of them, or a pharmaceutical composition containing it can be evaluated. . .

CLM What is claimed is:

. . . 25. The composition according to claim 24, which is an agent for treating or preventing a disease to which an ***adenosine*** ***receptor*** relates.

28. The composition according to claim 24, which is an ***adenosine*** ***receptor*** antagonist.

. . . 1 or a pharmacologically acceptable salt thereof for producing an agent for treating or preventing a disease to which an ***adenosine*** ***receptor*** relates.

40. A method of treating or preventing a disease to which an ***adenosine*** ***receptor*** relates, by administering a pharmacologically effective dose of the compound according to claim 1 or a pharmacologically acceptable salt thereof. . .

L4 ANSWER 5 OF 7 USPATFULL on STN

ACCESSION NUMBER: 2003:244969 USPATFULL

TITLE: Medicinal compositions promoting bowel movement

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| | NUMBER | KIND | DATE | |
|---|---|---|---|---|
| PATENT INFORMATION: | US 2003171383 | A1 | 20030911 | |
| APPLICATION INFO.: | US 2002-257091 | A1 | 20021009 | (10) |
| | WO 2001-JP3643 | | 20010426 | |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | JP 2000-126489 | 20000426 |
| | JP 2000-220124 | 20000721 |

DOCUMENT TYPE: Utility

FILE SEGMENT: APPLICATION

LEGAL REPRESENTATIVE: BIRCH STEWART KOLASCH & BIRCH, PO BOX 747, FALLS CHURCH, VA, 22040-0747

NUMBER OF CLAIMS: 31

EXEMPLARY CLAIM: 1

LINE COUNT: 2491

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

SUMM . . . suggesting the relationship thereof with central nerve diseases, cardiovascular diseases, inflammatory diseases, respiratory diseases, immune diseases etc., so usefulness of ***adenosine*** ***receptor*** agonists/antagonists against these diseases is expected. In addition to WO94/16702 supra, the relationship between the adenosine receptors and the intestinal. . .

SUMM . . . defecation-promoting agent according to the above-mentioned (1)

2-amino-4-(2-furyl)-5-(4-pyridyl)pyrimidine, ***3*** - ***n*** - ***propylxanthine*** , theophylline, caffeine, 1,3-dipropylxanthine, enprophylline, 1-methyl-3-isobutylxanthine, paraxanthine, 8-phenyltheophylline, 1,3-diethyl-8-phenylxanthine, 8-[4-[[[[(2-aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-dipropylxanthine, 8-[4-[[[methyl-(2-dimethylaminoethyl)-amino]sulfonyl]phenyl]-1,3-dipropylxanthine, 1,3-dimethyl-8-(p-sulfophenyl)xanthine and 1,3-dipropyl-8-(p-sulfophenyl)xanthine, (11) use of a compound having an. . .

SUMM [0030] In this-specification, the "antagonism" refers to the action of inactivating by blocking the interaction of the ***adenosine*** ***receptor*** with its ligand (adenosine), that is, by blocking the binding of the ligand to the receptor. The "compound having an. . . antagonism" refers to a compound having the action of inactivating by blocking the binding of the ligand (adnosine) to the ***adenosine*** ***receptor*** .

SUMM . . . receptor antagonists, while KW6002 is known as a selective A.sub.2a receptor antagonist. The ability of these compounds to bind to ***adenosine*** ***receptor*** subtype and the inhibitory ability thereof are shown below (Table 6). KF20274 was produced by a process described in J.. . .

SUMM [0041] (4) Inhibitory Effect of ***Adenosine*** ***Receptor*** Antagonist on Suppressing Action of NECA on Carbachol-Stimulated Contraction of the Colon Tract

SUMM . . . presence of 0.3 .mu.M Carbachol only was regarded as 100% contraction, the contraction in the presence of each of the ***adenosine*** ***receptor*** antagonists was determined. In the experiment, 3 samples were used.

SUMM . . . operation 2), the colon tract showed contraction in a manner dependent on the concentration of Carbachol (Table 1). When the ***adenosine*** ***receptor*** agonist NECA was added thereto (the above operation 3), its inhibitory effect on the contraction was observed in a manner. . . distributed in smooth muscles, thus suggesting the possibility of its direct action on smooth muscles. Further, when each antagonist for ***adenosine*** ***receptor*** was added to this system (the above operation 4), Compound I inhibited the suppressing effect of NECA on the contraction,. . .

SUMM [0055] The ability of the compound to bind to and the ability thereof to inhibit each subtype of ***adenosine*** ***receptor*** was measured in a known method described below.

SUMM . . . to which the present invention belongs can measure the ability of any compounds to bind to, or to inhibit, the ***adenosine*** ***receptor*** subtype thereby identifying a compound having an A.sub.2 receptor antagonism and a compound having an A.sub.2b receptor antagonism.

SUMM [0094] (13) 1) ***3*** - ***n*** - ***Propylxanthine*** ; 2) 1,3-dipropyl-8-(p-acrylic)phenylxanthine; 3) 1,3-dipropyl-8-cyclopentylxanthine; 4) 1,3-dipropyl-8-(p-sulfophenyl)xanthine; 5) xanthinamine analogues; 6) 1,3-dipropyl-8-[2-(5,6-epoxynorbonyl)]xanthine; and 7) 1,3-dimethylcyclohexyl-8-phenyl(4-acrylate)xanthine (U.S. Pat. No. 6,060,481)

SUMM [0111] (16) 1) ***3*** - ***n*** - ***Propylxanthine*** ; 2) 1,3-dipropyl-8-(p-acrylic)phenylxanthine; 3) 1,3-dipropyl-8-cyclopentylxanthine; 4) 1,3-dipropyl-8-(p-sulfophenyl)xanthine; 5) a xanthineamine congener; and 6) 1,3-dipropyl-8-[2-(5,6-epoxynorbonyl)]xanthine (U.S. Pat. No. 6,060,481).

DETD . . . of the adenosine A.sub.2b receptor-inhibiting compound which was identified by measuring the binding ability and inhibitory ability thereof to the ***adenosine*** ***receptor*** in the above method, a salt thereof, a hydrate of them, or a pharmaceutical composition containing it can be evaluated. . .

CLM What is claimed is:

. . . The defecation-promoting agent according to claim 1 or 2, wherein the compound is at least one compound selected from 2-amino-4-(2-furyl)-5-(4-pyridyl)pyrimidine, ***3*** - ***n*** - ***propylxanthine*** , theophylline, caffeine, 1,3-dipropylxanthine, enprophylline, 1-methyl-3-isobutylxanthine, paraxanthine, 8-phenyltheophylline, 1,3-diethyl-8-phenylxanthine, 8-[4-[[[[(2-aminoethyl)amino]carbonyl]methyl]oxy]phenyl]-1,3-dipropylxanthine, 8-[4-[[[methyl-(2-dimethylaminoethyl)-amino]sulfonyl]phenyl]-1,3-dipropylxanthine, 1,3-dimethyl-8-(p-sulfophenyl)xanthine and 1,3-dipropyl-8-(p-sulfophenyl)xanthine.

L4 ANSWER 6 OF 7 USPATFULL on STN
ACCESSION NUMBER: 2002:4163 USPATFULL

***receptor*** antagonists to mediate mammalian cell proliferation

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| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 2002002142 | A1 | 20020103 |
| APPLICATION INFO.: | US 2001-785895 | A1 | 20010216 (9) |

| | NUMBER | DATE |
|---|---|---|
| PRIORITY INFORMATION: | US 2000-183141P | 20000217 (60) |

DOCUMENT TYPE: Utility
FILE SEGMENT: APPLICATION
LEGAL REPRESENTATIVE: A. Blair Hughes, McDonnell Boehnen Hulbert & Berghoff, 32nd Floor, 300 S. Wacker Drive, Chicago, IL, 60606
NUMBER OF CLAIMS: 18
EXEMPLARY CLAIM: 1
NUMBER OF DRAWINGS: 3 Drawing Page(s)
LINE COUNT: 453
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

TI Method for identifying and using A2B ***adenosine*** ***receptor*** antagonists to mediate mammalian cell proliferation

AB This invention concerns methods for identifying A.sub.2B ***adenosine*** ***receptor*** agonists and antagonists as well as methods for using A.sub.2B. ***adenosine*** ***receptor*** antagonists to treat cell proliferation orders mediated by the A.sub.2B ***adenosine*** ***receptor*** .

SUMM [0003] This invention concerns methods for identifying A.sub.2B ***adenosine*** ***receptor*** agonists and antagonists as well as methods for using A.sub.2B receptor antagonists to treat cell proliferation disorders mediated by the A.sub.2B ***adenosine*** ***receptor*** .

SUMM . . . A.sub.3. The nucleoside adenosine has been implicated in angiogenesis. Specifically, it has been demonstrated that adenosine activation of the A.sub.2 ***adenosine*** ***receptor*** (AdoR) increased cAMP accumulation, cell proliferation and VEGF expression in human retinal endothelial cells (HREC). It has been previously reported. . . .

SUMM [0007] In one embodiment, this invention is a method for inhibiting the proliferation of mammalian cells that express the A.sub.2B ***adenosine*** ***receptor*** comprising administering a therapeutically effective amount of an A.sub.2B ***adenosine*** ***receptor*** antagonist to the mammal.

SUMM [0008] In another embodiment, this invention is a method for assaying compounds to determine if they are A.sub.2B ***adenosine*** ***receptor*** antagonists or A.sub.2B ***adenosine*** ***receptor*** agonists. The method includes preparing a first and second sample of human retinal endothelial cells; adding a compound to be. . .

SUMM [0009] In yet another embodiment, this invention includes A.sub.2B ***adenosine*** ***receptor*** agonist or antagonist compounds identified by the methods of this invention.

DRWD . . . course of NECA (10 .mu.mol/L) induced HREC proliferation. The proliferation effect of NECA is completely blocked by either A.sub.2B-specific antagonists ***3*** - ***N*** - ***propylxanthine*** (10 .mu.mol/L) or JW-V1-08 (10 .mu.mol/L);

DRWD . . . 48 hr NECA supports extensive tube formation (4B). By contrast, the A.sub.2B selective antagonists JW-V1-08 at 10 .mu.mol/L (4C) and ***3*** - ***N*** - ***propylxanthine*** at 10 .mu.mol/L (4D) both diminished NECA-induced tube formation. All micrographs are typical of results seen for cells from three separate donors.

SUMMARY OF ABBREVIATIONS

| | |
|---|---|
| HREC | Human retinal endothelial cells |
| AdoR | ***Adenosine*** ***receptor*** |
| NECA | 5'-N-ethylcarboxamido-adenosine |
| ADA | Adenosine deaminase |
| JW-V1-08 | 3-isobutyl-8-pyrrolidinoxanthine |
| LDL | Low density lipoprotein |
| SFM | Serum Free Medium |
| VEGF | Vascular endothelial growth factor |

A.sub.2B ***adenosine*** ***receptor*** antagonists. This invention also includes A.sub.2B ***adenosine*** ***receptor*** antagonists identified by the methods of this invention as well as methods for inhibiting cell proliferation in mammals using A.sub.2B ***adenosine*** ***receptor*** antagonists.

DETD [0014] One aspect of this invention is methods for screening and identifying compounds that are A.sub.2B ***adenosine*** ***receptor*** agonists and antagonists. The compounds identified by the methods of this invention may include organic compounds, inorganic compounds, oligonucleotides, antisense. . .

DETD [0015] One method for evaluating compounds as potential A.sub.2B ***adenosine*** ***receptor*** antagonists or agonists of this invention is an in vitro assay that measures the ability of a compound to promote. . . a standard compound. Compounds that stimulate the growth of human retinal endothelial cells in comparison to the standard are A.sub.2B ***adenosine*** ***receptor*** agonists while compounds that inhibit human endothelial cells growth in comparison to the standard are A.sub.2B ***adenosine*** ***receptor*** antagonists.

DETD [0016] A second assay that is useful for identifying A.sub.2B ***adenosine*** ***receptor*** antagonists and agonists is an in vivo mouse assay. In the mouse model, one week old C57BL/6J mice are exposed. . . tufts in the eyes of an untreated mouse. Compounds that inhibit the growth of neovascular tufts in vivo are A.sub.2B ***adenosine*** ***receptor*** antagonists.

DETD [0017] Another important aspect of this invention is the discovery that A.sub.2B ***adenosine*** ***receptor*** antagonists are useful in treating mammalian cell proliferation disorders. Such disorders include, but are not limited to vascular endothelial cell. . .

DETD [0018] We have found that A.sub.2B ***adenosine*** ***receptor*** antagonists are particularly useful for inhibiting the growth of vascular endothelial cells which include but not limited to coronary endothelial. . . diseases associated the proliferation of retinal endothelial cells (aberrant neovascularization) such as diabetic retinopathy and retinopathy of prematurity. The A.sub.2B ***adenosine*** ***receptor*** antagonists used may be a non-selective A.sub.2B ***adenosine*** ***receptor*** antagonists, they may be a selective A.sub.2B ***adenosine*** ***receptor*** antagonists or they may include a combination of A.sub.2B ***adenosine*** ***receptor*** antagonists.

DETD [0019] Methods of this invention for inhibiting cell proliferation and in particular inhibiting endothelial cell proliferation using A.sub.2B ***adenosine*** ***receptor*** antagonists are applicable to any mammal. However, it is preferred that the methods of this invention are used to treat. . . humans. The methods of this invention are performed using pharmaceutically effective amounts of one or more compounds that are A.sub.2B ***adenosine*** ***receptor*** antagonists. Depending on their intended use, the compositions may be in the form of solid, semi-solid or liquid dosage forms,. . .

DETD . . . cells, the compositions of this invention may be incorporated into eye drops by, for example, combining one or more A.sub.2B ***adenosine*** ***receptor*** antagonists with a physiologically compatible saline solution or gel which is then applied directly to the eyes on a regular. . .

DETD [0024] Generally, A.sub.2B ***adenosine*** ***receptor*** antagonists will be administered in the methods of this invention in a therapeutically effective amount, i.e., a dosage sufficient to. . . of administration, the affliction being treated, and the degree of affliction being treated. For example, eye drops including an A.sub.2B ***adenosine*** ***receptor*** antagonists can be administered on a regular schedule of from once to 6 times a day or even more frequently. . .

DETD [0025] The administration of A.sub.2B ***adenosine*** ***receptor*** antagonists to mammals to treat cell proliferation disorders is not limited to those methods disclosed above that broadly includes any. . .

DETD . . . with 1 U/mL adenosine deaminase (ADA) for 30 min. Cells were the exposed to NECA (10 .mu.mol/L) with or without ***3*** - ***N*** - ***propylxanthine*** (10 .mu.mol/L) or JW-V1-08 (10 .mu.mol/L), which exhibit greater selectivity for the A.sub.2B receptor than other available antagonists. Controls were. . .

DETD . . . the chamber of 2h. The chambers were then placed upright and exposed to NECA alone (10 .mu.mol/L), NECA combined with ***3*** - ***N*** - ***propylxanthine*** (10 .mu.mol/L), JW-V1-08 (10 .mu.mol/L) or the non-selective AdoR antagonist xanthine amine congener (XAC, 10 .mu.mol/L) in a 50 .mu.L. . .

days. Both of the selective A.sub.2B, AdoR antagonists tested, ***3*** - ***N*** - ***propylxanthine*** at 10 .mu.mol/L and JW-V1-08 at 10 .mu.mol/L, completely block the proliferative effect of NECA (FIG. 1A).

DETD . . . AdoR antagonist XAC abolished NECA-stimulated migration of HREC. Likewise, co-addition of NECA with either the selective A.sub.2B antagonists JW-V1-08 or ***3*** - ***N*** - ***propylxanthine*** also antagonized the stimulatory effect of NECA on chemotaxis (FIG. 1B). Neither NECA alone nor NECA in combination with the. . .

DETD . . . NECA (10 .mu.mol/L) treatment supported extensive tube formation (FIG. 2B) that was inhibited 2by JW-V1-08 (FIG. 2C). At 48 hr ***3*** - ***N*** - ***propylxanthine*** (FIG. 2D) inhibited tube formation, resulting in fewer tubes of shorter length.

DETD . . . increased tube length more than 2-fold greater than untreated cells (74.2 .+-.2.4 versus 35.7.+-.1.6, respectively, p<0.01). The addition of either ***3*** - ***N*** - ***propylxanthine*** or JW-V1-08 decreased, but did not completely negate, the NECA-induced tube length (53.7.+-.0.9 and 66.+-.1.2, respectively, both p<0.01).

DETD [0045] Summary: NECA induced proliferation in a concentration-dependent manner that was inhibited by the selective A.sub.2B AdoR antagonists ***3*** - ***N*** - ***propylxanthine*** and JW-V1-08. NECA stimulated chemotaxis in a concentration-dependent manner. Both antagonists blocked the effect of NECA on migration. NECA enhanced. .

.

CLM What is claimed is:

1. A method for inhibiting the proliferation of mammalian cells that express the A.sub.2B ***adenosine*** ***receptor*** comprising administering a therapeutically effective amount of an A.sub.2B ***adenosine*** ***receptor*** antagonist to the mammal.

2. The method of claim 1 wherein the cells that express the A.sub.2B ***adenosine*** ***receptor*** are vascular endothelial cells.

3. The method of claim 2 wherein the vascular endothelial cells that express the A.sub.2B ***adenosine*** ***receptor*** are selected from the group consisting of coronary endothelial cells, endothelial cells from the vascular bed.

6. The method of claim 1 wherein the A.sub.2B ***adenosine*** ***receptor*** antagonist inhibits the expression of vascular endothelial cell growth factor (VEGF).

7. The method of claim 1 wherein the A.sub.2B ***adenosine*** ***receptor*** antagonist is an A.sub.2B ***adenosine*** ***receptor*** antisense oligonucleotide.

8. The method of claim 1 wherein the A.sub.2B ***adenosine*** ***receptor*** antagonist is an A.sub.2B-specific ribozyme.

9. The method of claim 1 wherein the A.sub.2B ***adenosine*** ***receptor*** antagonist is a non-selective ***adenosine*** ***receptor*** antagonist.

10. The method of claim 1 wherein the A.sub.2B ***adenosine*** ***receptor*** antagonist is a selective A.sub.2B ***adenosine*** ***receptor*** antagonist.

11. The method of claim 1 wherein the A.sub.2B ***adenosine*** ***receptor*** antagonist is administered in an amount raging from about 1 microgram/kg to about 50 miligrams/kg.

12. The method of claim 1 wherein the adenosine A.sub.2B ***adenosine*** ***receptor*** antagonist is administered in an amount ranging from about 1 microgram/kg to about 10 miligrams/kg.

13. The method of claim 1 wherein the A.sub.2B ***adenosine*** ***receptor*** antagonist is administered by a method selected from the group consisting of orally, nasally, transdermally, by bolus, intravenously, in eye. . .

14. The method of claim 1 wherein the A.sub.2B ***adenosine*** ***receptor*** agonist is administered in eye drops.

16. A method for assaying compounds to determine if they are A.sub.2B ***adenosine*** ***receptor*** antagonists or A.sub.2B ***adenosine*** ***receptor*** agonists comprising the steps of: a. preparing a first and second sample of human retinal endothelial cells; b. adding a. . .

compound identified by the method of claim 16 wherein the compound caused fewer new cells to grow in the. . .
18. An A.sub.2B ***adenosine*** ***receptor*** agonist compound identified by the method of claim 16 wherein the compound caused more new cells to grow in the. . .

L4 ANSWER 7 OF 7 USPATFULL on STN

| | |
|---|---|
| ACCESSION NUMBER: | 88:72477 USPATFULL |
| TITLE: | 8-arylxanthines |
| INVENTOR(S): | Rzeszotarski, Waclaw J., Millersville, MD, United States<br>Hicks, Rickey P., Columbia, MD, United States<br>Erickson, Ronald H., Baltimore, MD, United States |
| PATENT ASSIGNEE(S): | Marion Laboratories, Inc., Kansas City, MO, United States (U.S. corporation) |

| | NUMBER | KIND | DATE |
|---|---|---|---|
| PATENT INFORMATION: | US 4783530 | | 19881108 |
| APPLICATION INFO.: | US 1987-108990 | | 19871001 (7) |

| | |
|---|---|
| RELATED APPLN. INFO.: | Continuation-in-part of Ser. No. US 1986-931620, filed on 13 Nov 1986, now abandoned |
| DOCUMENT TYPE: | Utility |
| FILE SEGMENT: | Granted |
| PRIMARY EXAMINER: | Rizzo, Nicholas S. |
| LEGAL REPRESENTATIVE: | Dewey, Ballantine, Busby, Palmer & Wood |
| NUMBER OF CLAIMS: | 8 |
| EXEMPLARY CLAIM: | 1 |
| LINE COUNT: | 705 |

CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The compounds are potent ***adenosine*** ***receptor*** antagonists having relatively low lipophilicity. The compounds are intended for use as bronchodilators and cardiotonics.

SUMM This invention relates to arylxanthines which are relatively potent ***adenosine*** ***receptor*** antagonists with enhanced water solubility and beneficial pharmacological activity. The are 1,3-alkyl-substituted-8-(3,4-,3- or 4-substituted phenyl) xanthines and the pharmaceutically acceptable. . .

SUMM . . . causing an increase in heart rate or peripheral pressure. From that point of view selectivity toward the A.sub.1 --subclass of ***adenosine*** ***receptor*** is highly desired.

SUMM . . . (I). ##STR1## This compound was reported 70,000 times more potent [at the receptor level] than theophylline and selective toward A.sub.1 -- ***adenosine*** ***receptor*** . It is also approximately 40,000 times more lipophilic. Calculation of its partition coefficient using Rekker's hydrophobic fragmental constants gives an. . .

SUMM This invention relates to novel 8-phenylxanthines which are relatively potent ***adenosine*** ***receptor*** antagonists while being relatively free of side effects. Specifically, this invention provides compounds of the formula: ##STR3## wherein R.sub.1 and. . .

SUMM 1. high affinity to ***adenosine*** ***receptor*** ,

SUMM 2. high selectivity toward A.sub.1 -- ***adenosine*** ***receptor*** ,

SUMM The compounds would be formulated and used in pharmaceutical compositions typically used with xanthines and other ***adenosine*** ***receptor*** antagonists. These compositions would contain amounts of the compounds of the invention sufficient to result in delivery to a patient. . .

DETD 1-Methyl-8-(4-cyanophenyl)- ***3*** - ***n*** - ***propylxanthine*** . 6-Amino-3-methyl-5-(4-cyanophenyl)imino-1-n-propyluracil (5.00 g, 17.4 mmol) is dissolved in 75 ml of glyme and 4.2 ml (21.4 mmol) of diisopropylazodicarboxylate is. . . then filtered hot. The filter cake is washed with glyme (3.times.20 ml) and ether (3.times.30 ml) and airdried to give 1-methyl-8-(4-cyanophenyl)- ***3*** - ***n*** - ***propylxanthine*** .

DETD The following examples contain tests which reflect the potency of the compounds of the invention as ***adenosine*** ***receptor*** antagonists.

DETD ***Adenosine*** ***Receptor*** Binding Assay. The potency of 8-arylxanthine compounds to inhibit the specific binding of [.sup.3 H]-cyclohexyladenosine ([.sup.3 H]CHA) to ***adenosine*** ***receptor*** sites on guinea pig cortical membranes was examined using standard in vitro ligand binding techniques. The assay protocol utilized in. . .

DETD ***Adenosine*** ***Receptor*** Linked Adenylate Cyclase. The

by a modification of the procedure of. . .

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Executing the logoff script...

=> LOG H

| COST IN U.S. DOLLARS | SINCE FILE ENTRY | TOTAL SESSION |
|---|---|---|
| FULL ESTIMATED COST | 34.77 | 34.98 |

| DISCOUNT AMOUNTS (FOR QUALIFYING ACCOUNTS) | SINCE FILE ENTRY | TOTAL SESSION |
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